Remarks

The Office Action mailed April 22, 2004 has been received and reviewed. Claims 70 and 72 having been amended and claims 73-80 having been added, the pending claims are claims 44-48, 50-54, 56-60, 64-80.

Claims 70 and 72 have been amended to further clarify that an end of the universal oligonucleotide probe can be "directly adjacent" to an end of the mutant polymorphism oligonucleotide probe, which is supported by the specification at, for example, page 16, line 5.

Support for new claims 73-80 can be found in the original claims and throughout the specification.

Reconsideration and withdrawal of the rejections of the claims, in view of the remarks and amendments presented herein, is respectfully requested.

Objection to the Specification

The Examiner objected to the specification alleging that essential material was improperly incorporated into the specification by reference. However, the Examiner has not indicated what material is considered to be essential.

Applicant emphasizes that nonessential material may be incorporated by reference to (1) patents or applications published by the United States or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications, or (3) non-patent publications (M.P.E.P. § 608.01(p)(A)). Accordingly, Applicant submits that incorporation by reference of nonessential material is proper and that the Examiner has failed to identify any essential material in the documents incorporated by reference.

In the event that the Examiner maintains the objection to the specification, the Examiner is respectfully requested to specifically indicate what material is considered to be essential so that Applicant can adequately address the Examiner's objection.

Objection to the Drawings

The Examiner objected to the drawings because the last circular oligonucleotide (Seq ID No. 21) in Figure 4A includes an obvious typographical error: a lower case "s" is incorrectly represented by a period (".") at the bottom of the representation.

The Examiner also objected to the drawings because the drawing of the product of "ligation of duplex DNA" (Seq. ID No 10) in Figure 4a incorrectly illustrates hydrogen bonding between bases in the middle of the paired sequences.

Applicant sincerely thanks the Examiner for reviewing the figures thoroughly and for providing Applicant with constructive input. In response to the Examiner's objections, Applicant has amended Figure 4a to correct the indicated obvious typographical error and to show proper hydrogen bonding between bases, which would be apparent to one of skill in the art.

Rejections under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 44-48, 50-54, 56-60, and 64-72 under 35 U.S.C. § 112, first paragraph, alleging that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner alleged that the term "oligonucleotide containing an α-haloacyl group" and the term "leaving group" do not satisfy the written description requirement as put forth in *Reagents of the University of California v. Eli Lilly*, 43 U.S.P.Q.2d 1398, 1406 (Fed. Cir. 1997). This rejection is respectfully traversed.

Applicant emphasizes that the cited case relates to polynucleotides of undisclosed nucleotide sequence that code for proteins identified by function. In contrast, the present claims are directed to methods that utilize oligonucleotide probes that are complimentary to a region on a target polynucleotide. Thus, the nucleotide sequence, and therefore the structure, of the claimed oligonucleotide probes is understood by those of skill in the art to correspond to the complement of a target polynucleotide.

The Examiner also alleged that use of the term "leaving group" is indefinite. Applicant submits that the term "leaving group" is defined within the specification as an atom or group attached to carbon such that on nucleophilic attack of the carbon atom by the nucleophile (sulfur, selenium or tellurium) of the modified phosphoryl group, the leaving group leaves as an anion (e.g., page 12, lines 18-20). Any leaving group capable of participating in an S_N2 reaction involving sulfur, selenium, or tellurium as the nucleophile can be utilized (e.g., page 12, lines 16-18). Furthermore, the term "leaving group" is well known in the art as illustrated, for example, in EXHIBIT A. Therefore, Applicant submits that the term "leaving group" has been defined and is known in the art.

Applicant respectfully submits that the claims satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, and request reconsideration and withdrawal of the rejections of the claims.

The Examiner rejected claims 44-48, 50-54, 56-60, and 64-72 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner alleged that the full scope of the claims cannot be practiced without undue experimentation. This rejection is respectfully traversed. The following paragraphs address the Examiner's analysis provided in the Office Action mailed 22 April 2004.

A. The Examiner alleged that the claims are overly broad. Applicant respectfully submits that the claims are not overly broad because the claims define the scope of the invention. The claims are directed to a method for detecting a genetic polymorphism in a target polynucleotide. The method utilizes oligonucleotide probes that are bound to a target polynucleotide and autoligate to form an autoligated oligonucleotide product that is detected. In some embodiments, the oligonucleotide probes can be positioned directly adjacent to each other. In other embodiments a 1-2 base gap or overlap can exist between the oligonucleotide probes. These aspects of the invention are put forth in the claims.

B. The nature of the invention relates to hybridization of nucleic acids. Methods utilizing hybridization of nucleic acids are well researched and developed. The U.S. Patent and Trademark Office has long recognized the patentability of such methods, see for example U.S. Patent No. 5,688,641, a copy of which is attached for the Examiner's convenience (EXHIBIT B).

C. Applicants respectfully submit that the art cited by the Examiner indicates that the state of the art is high.

D. The skill level of those in the art is high.

E. As stated by the Examiner, the level of predictability in the art is high with regard to situations where the reactive groups are adjacent. However, the Examiner alleged that there is no prior art teaching of a reaction occurring when there is either a gap of one or two bases or an overlap of one or two bases. Applicant respectfully submits that the present specification provides adequate enablement for one of skill in the art to practice hydridization methods as claimed. The Examiner also asserted that there is no teaching of how to incorporate a phosphorotelluroate at the 3'-position of an oligonucleotide or how to use such an oligonucleotide. Applicant submits that one of skill in the art could prepare such oligonucleotide probes for use in the invention using routine synthetic methods known in the art.

F. The Examiner alleged that the amount of direction provided by the inventor is limited to how to make and use an oligonucleotide including a 3'-phosphorothioate or a 3'-phosphoroselenoate and how to make and use an oligonucleotide including only a 5'-deoxy-5'-iodonucleoside in a chemical ligation process. The Examiner also alleged that the specification does not provide sufficient enablement for oligonucleotides containing an α-haloacyl group, any leaving group at the 5'-location other than the iodo group, or conditions used when ligation occurs across a gap or overlap of one to two bases. Applicant respectfully emphasizes that the specification provides numerous chemically modified autoligating oligonucleotides (e.g., page 11, line 22 to page 15, line 8). Furthermore, as stated by the Examiner, the prior art includes multiple reports that auto chemical ligation reaction occurs between co-hybridized oligonucleotides. Accordingly, Applicant submits that one of skill in the art, in view of the

present specification, could practice the presently claimed invention without undue experimentation. In addition, the specification provides working examples of autoligation between oligonucleotides that are separated by a gap (e.g., Figures 8-11a).

G. The Examiner alleged that the existence of working examples is limited. Applicant emphasizes that the specification provides numerous working examples of the invention as illustrated in the figures and the examples section (pages 25-61). In addition, Applicant respectfully emphasizes that oligonucleotide probes that are shorter than a 7-mer may be used as they transiently hybridize to a template polynucleotide and can therefore form an autoligated product with a second oligonucleotide probe. Applicants emphasize that hybridization between single stranded termini that are 1-6 basepairs in length is well known as illustrated in EXHIBIT C (attached hereto).

H. The Examiner alleged that the quantity of experimentation necessary to make or use the invention is excessive. Applicant emphasizes that when analyzing whether it requires "undue experimentation" to practice claimed methods, the key word is "undue" not "experimentation." *In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). A considerable amount of experimentation is permissible if it is merely routine, or the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should take. *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (Bd. App. 1982). Applicant emphasizes that working examples have been provided and a considerable amount of guidance is provided within the specification and the prior art, as previously stated.

The first paragraph of 35 U.S.C. § 112 requires no more than a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. The above evaluation of the factual considerations outlined by the Federal Circuit in *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) demonstrates that the claimed invention can be practiced without undue or unreasonable experimentation. Accordingly, Applicant respectfully submits that the instant application satisfies the enablement requirements of 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 44-48, 50-54, 56-60, and 64-72 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner alleged that use of the term "comprising" within the claims causes the claims to be indefinite because the term refers to chemically modified starting materials and products and by such reference implies the absence of a complete description of the structural features of said chemically modified starting materials and products. This rejection is respectfully traversed.

Regarding the requirement under 35 U.S.C. § 112, second paragraph, for particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention, the M.P.E.P. states that "[t]he primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent." M.P.E.P. § 2173.

First, Applicant respectfully submits that the use of "comprising" or "having" as a transitional phrase is proper as acknowledged by the M.P.E.P. (*see, for example*, M.P.E.P. §2111.03), which states that the term "comprising" is synonymous with "including," "containing," or "characterized by." Further, Applicant respectfully notes that the United States Patent and Trademark Office has issued numerous patents with claims reciting an "oligonucleotide comprising" a specific element. *See, for example*, U.S. Pat. Nos. 6,020,483, claim 16 (L. Eric Crane, Primary Examiner) (EXHIBIT D); 6,111,086, claim 1 (James O. Wilson, Primary Examiner) (EXHIBIT E); and 6,090,932, claim 16 (James O. Wilson, Primary Examiner) (EXHIBIT F). Thus, Applicant respectfully submits that the term "comprising" is clear, and that the present claims distinctly define Applicant's invention using inclusive or open-ended language.

Second, Applicant respectfully submits that the scope of claims 44-48, 50-54, 56-60, and 64-72, which recite the term "comprising," is clear and informs the public of the boundaries of what constitutes infringement of the patent. Clearly, the method recited in the claims including

oligonucleotides comprising the 3' and/or 5' ends recited in the present claims is within the boundaries of the present claims.

Moreover, the M.P.E.P. states that

> [t]he examiner's focus during examination of claims for compliance with the requirement for definiteness of 35 U.S.C. 112, second paragraph is whether the claim meets the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available. When the examiner is satisfied that patentable subject matter is disclosed, and it is apparent to the examiner that the claims are directed to such patentable subject matter, he or she should allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness. Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire. Examiners are encouraged to suggest claim language to applicants to improve the clarity or precision of the language used, but should not reject claims or insist on their own preferences if other modes of expression selected by applicants satisfy the statutory requirement. (M.P.E.P. §2173.02; emphasis in original).

Thus, based on the remarks presented herein above, Applicant respectfully submits that claims 44-48, 50-54, 56-60, and 64-72 particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 44-48, 50-54, 56-60, and 67-72 under 35 U.S.C. § 102 as being anticipated by Letsinger (U.S. Patent No. 5,780,613), Northwestern (WO 96/35699), Letsinger (U.S. Patent No. 5,681,943) and Gryaznov (U.S. Patent No. 5,571,903). These rejections are respectfully traversed.

A claim is anticipated only if **each and every element** as set forth in the claim is found, either expressly or inherently described, in a single prior art reference (emphasis added)

(M.P.E.P. § 2131, citing *Verdegaal Bros. V. Union Oil Co. of California*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987)).

Claims 44-48 are directed to a method for detecting a genetic polymorphism in a target polynucleotide. The method includes providing a mutant polymorphism oligonucleotide probe and providing a universal oligonucleotide probe such that, when both probes are bound to the target polynucleotide, an end of the universal oligonucleotide probe is **not directly adjacent** to an end of the mutant polymorphism oligonucleotide probe (e.g., claims 44 and 65), or there is a gap of 1 or 2 bases or a 1 or 2 nucleotide overlap between an end of the universal oligonucleotide probe and an end of the mutant polymorphism oligonucleotide probe (e.g., claims 64-66).

Claims 50-54 and 67-69 are directed to a method for detecting a genetic polymorphism in a target polynucleotide including contacting the target polynucleotide with the **universal oligonucleotide probe**, the **wild-type polymorphism oligonucleotide probe** and the **mutant polymorphism oligonucleotide probe** to yield an autoligated oligonucleotide product including the universal oligonucleotide probe and **either** the mutant polymorphism oligonucleotide probe **or** the wild-type polymorphism oligonucleotide probe and detecting the presence of the autoligated oligonucleotide product.

Claims 56-60 and 70-72 are directed to a method for detecting a **genetic polymorphism** in a **target RNA** including contacting the target RNA with the universal oligonucleotide probe and the mutant polymorphism oligonucleotide probe to yield an autoligated oligonucleotide product including the universal oligonucleotide probe and the mutant polymorphism probe and detecting the presence of the autoligated oligonucleotide product.

Letsinger (U.S. Patent No. 5,780,613)

Letsinger discloses "[a] method of autoligating self-assembled oligonucleotide blocks . . . . The method includes the step of displacing a 5' displaceable group by a 3' thiophosphoryl group to form an –OP(O)(O^-)S– internucleoside linkage" (abstract). Letsinger

discloses a "ligation scheme in which an oligonucleotide containing a 3' phosphoryl group . . . and another oligonucleotide . . . containing a displaceable group at a terminal 5' carbon atom are aligned and ligated . . . on a complementary template oligonucleotide" (column 3, lines 1-6), in which the two modified oligonucleotides are illustrated in Figure 1 as being hybridized **directly adjacent** to each other on the complementary template oligonucleotide. Alternatively, Letsinger discloses that "ligation chemistry can be employed to close a gap formed by a single linear oligonucleotide" (column 3, lines 17-19), as illustrated in Figures 3, 6, and 9 with the 5' and 3' ends being **directly adjacent** to each other.

The Examiner refers Applicant to the abstract; pages 13 and 17; and Figures 1, 5, 9, 12 and 13 of Letsinger. Applicant requests clarification with regard to the Examiner's citation of pages 13 and 17, as U.S. Patent No. 5,780,613 does not include numbered pages, or a column numbered 17. Accordingly, the Examiner is respectfully requested to clarify the specific location of subject matter which is alleged to anticipate the claims in the event that the rejection is maintained.

Applicant respectfully submits that the specific examples that the Examiner points to in Letsinger disclose the use of oligonucleotides that are **directly adjacent** to each other when bound to a template. However, Letsinger fails to teach a method that utilizes oligonucleotide probes that are **not directly adjacent** (e.g., claims 44-48). Letsinger also fails to teach a method that includes contacting the target polynucleotide with the **universal oligonucleotide** probe, the **wild-type polymorphism oligonucleotide** probe and the **mutant polymorphism oligonucleotide** probe to yield an autoligated oligonucleotide product including the universal oligonucleotide probe and **either** the mutant polymorphism oligonucleotide probe **or** the wild-type polymorphism oligonucleotide probe; and detecting the presence of the autoligated oligonucleotide product (e.g., claims 50-54 and 67-69). Furthermore, Letsinger fails to teach a method for detecting a **genetic polymorphism** in a **target RNA** that includes contacting the target RNA with the **universal oligonucleotide** probe and the **mutant polymorphism oligonucleotide** probe to yield an autoligated oligonucleotide product including the universal

oligonucleotide probe and the mutant polymorphism oligonucleotide probe; and detecting the presence of the autoligated oligonucleotide product (e.g., claims 56-60 and 70-72).

Applicant respectfully submits that Letsinger fails to teach each and every element as set forth in the claim and therefore fails to anticipate the claims for the above mentioned reasons. Accordingly, the Examiner is respectfully requested to withdraw the rejections of the claims.

Northwestern (WO 96/35699)

Northwestern discloses "[a] method for hybridizing nucleic acids [including] the steps of reversibly binding a first oligomer to a target oligo- or polynucleotide including base units complementary to base units of the oligonucleotide, reversibly binding a second oligomer to the target oligo- or polynucleotide including base units complementary to base units of the oligonucleotide adjacent to the first oligomer, and wherein one of the oligomers includes a nucleotide having a first reactive group proximate to a nucleotide of the other oligomer which includes a second reactive group capable of spontaneously forming a covalent bond with the first reactive group" (abstract). Northwestern further discloses that "[t]wo oligonucleotides, in which one is terminated by a phosphorothioate group and the other by a bromoacetylamino group, spontaneously couple rapidly and efficiently, with formation of an internucleoside phosphorylthioacetylamino link (-OP(O) (O) (O)SCH2C (O)NH-), when **bound contiguously** on a matching oligonucleotide template" (page 18, lines 3-9; emphasis added). Northwestern even further discloses "(a) reversibly binding a first oligomer to a target oligo- or polynucleotide including base units complementary to base units of the oligonucleotide, wherein the first oligomer has a relatively low affinity and high selectivity to the target polynucleotide; (b) reversibly binding a second oligomer to the target oligo- or polynucleotide including base units complementary to base units of the oligonucleotide **adjacent** to the first oligomer, wherein the second oligomer has high affinity for the target polynucleotide, and wherein one of the oligomers includes a nucleotide having a first reactive group proximate to a nucleotide of the other oligomer which includes a second reactive group capable of spontaneously forming a

covalent bond with the first reactive group" (claim 1; emphasis added), as illustrated in Figures 2-4 with the reactive groups being **directly adjacent** to each other. Northwestern also discloses the use of three oligonucleotides that form a product that contains all three oligonucleotides **linked contiguously** as illustrated at, for example, page 17, lines 9-26.

Applicant respectfully submits that the specific examples that the Examiner points to in Northwestern disclose the use of oligonucleotides that are **directly adjacent** to each other when bound to a template as is further indicated within the specification (i.e., page 10, line 29; page 18, line 8; claim 1). However, Northwestern fails to teach a method that utilizes oligonucleotide probes that are **not directly adjacent** (e.g., claims 44-48). Northwestern also fails to teach a method that includes contacting the target polynucleotide with the **universal oligonucleotide** probe, the **wild-type polymorphism oligonucleotide** probe and the **mutant polymorphism oligonucleotide** probe to yield an autoligated oligonucleotide product including the universal oligonucleotide probe and **either** the mutant polymorphism oligonucleotide probe **or** the wild-type polymorphism oligonucleotide probe; and detecting the presence of the autoligated oligonucleotide product (e.g., claims 50-54 and 67-69). Furthermore, Northwestern fails to teach a method for detecting a **genetic polymorphism** in a **target RNA** that includes contacting the target RNA with the **universal oligonucleotide** probe and the **mutant polymorphism oligonucleotide** probe to yield an autoligated oligonucleotide product including the universal oligonucleotide probe and the mutant polymorphism oligonucleotide probe; and detecting the presence of the autoligated oligonucleotide product (e.g., claims 56-60 and 70-72).

Further, Northwestern fails to specifically disclose a mutant polymorphism oligonucleotide probe of less than 7 nucleotides in length (e.g., claims 50-54 and 67-69). Northwestern is silent regarding the length of the nucleotide probe, and the Examiner stated that "[t]he absence of any specified length means that all lengths are **covered**" (page 7 of Office Action mailed 22 April 2004). Applicant does not understand the Examiner's intended meaning of the above statement. *First*, while the term "covered" may be used colloquially in referring to claim scope, Applicant respectfully submits that the scope of the claims in the cited document is

not at issue in the present rejection. *Second*, Applicant respectfully submits that silence does not provide the positive disclosure required to support a rejection under 35 U.S.C. §102. For example, it is well known that the disclosure of a genus (e.g., a generic nucleotide probe of any length) does not anticipate a species (e.g., an oligonucleotide probe of less than 7 nucleotides in length) when the cited art does not specifically disclose the species. In the event that the present rejection is maintained, clarification of the Examiner's intended meaning of the above statement is respectfully requested in the next Official Communication.

Finally, the Examiner appears to be basing the anticipation rejection under 35 U.S.C. §102 on lack of enablement (paragraph spanning pages 7 to 8 of the Office Action mailed 22 April 2004). Applicant respectfully submits that enablement is an issue separate and distinct from anticipation. Further, Applicant has addressed herein any enablement issues in the remarks to the rejections under 35 U.S.C. §112, first paragraph.

Applicant respectfully submits that Northwestern fails to teach each and every element as set forth in the claim and therefore fails to anticipate the claims for the above mentioned reasons. Accordingly, the Examiner is respectfully requested to withdraw the rejections of the claims.

Letsinger (U.S. Patent No. 5,681,943)

Letsinger discloses "[a] method for increasing oligonucleotide selectivity comprising reversibly binding two oligonucleotides at **adjacent positions** to the bases on a complementary template and then spontaneously and irreversibly covalently joining said oligomers via two reactive groups brought into proximity of each other by the binding of the oligonucleotides, in the absence of added reagent or enzyme" (abstract; emphasis added). The adjacent positioning of the two oligonucleotides on the complementary template is taught throughout the specification (e.g., Figures 2-5; column 5, lines 32-35; column 6, lines 19-24; column 8, lines 46-52; claims 1 and 14). Letsinger also discloses the use of three oligonucleotides that form a product that contains all three oligonucleotides **linked contiguously** as illustrated at, for example, column 8, lines 22-36.

Applicant respectfully submits that the specific examples that the Examiner points to in Letsinger disclose the use of oligonucleotides that are **directly adjacent** to each other when bound to a template. However, Letsinger fails to teach a method that utilizes oligonucleotide probes that are **not directly adjacent** (e.g., claims 44-48). Letsinger also fails to teach a method that includes contacting the target polynucleotide with the **universal oligonucleotide** probe, the **wild-type polymorphism oligonucleotide** probe and the **mutant polymorphism oligonucleotide** probe to yield an autoligated oligonucleotide product including the universal oligonucleotide probe and **either** the mutant polymorphism oligonucleotide probe **or** the wild-type polymorphism oligonucleotide probe; and detecting the presence of the autoligated oligonucleotide product (e.g., claims 50-54 and 67-69). Furthermore, Letsinger fails to teach a method for detecting a **genetic polymorphism** in a **target RNA** that includes contacting the target RNA with the **universal oligonucleotide** probe and the **mutant polymorphism oligonucleotide** probe to yield an autoligated oligonucleotide product including the universal oligonucleotide probe and the mutant polymorphism oligonucleotide probe; and detecting the presence of the autoligated oligonucleotide product (e.g., claims 56-60 and 70-72).

Applicant respectfully submits that Letsinger fails to teach each and every element as set forth in the claim and therefore fails to anticipate the claims for the above mentioned reasons. Accordingly, the Examiner is respectfully requested to withdraw the rejections of the claims.

Gryaznov (U.S. Patent No. 5,571,903)

Gryaznov discloses "compositions and a method for delivering an antisense compound or probe to a target polynucleotide. The compositions of the invention comprise a plurality of compounds each having an oligonucleotide moiety from about 4 to 12 monomers in length whose 3' and/or 5' termini have been modified by the addition of one or more terminal binding moieties. Whenever the oligonucleotide moieties specifically anneal to a target polynucleotide in a **contiguous end-to-end fashion**, the terminal binding moieties are capable of spontaneously interacting with one another to form a covalent linkages or stable complexes so that an effective

antisense compound or probe is formed" (abstract; emphasis added). The **contiguous end-to-end** positioning of the oligonucleotides to each other when bound to a target polynucleotide is taught throughout the specification including at, for example, column 3, lines 5-10 and claim 1.

Applicant respectfully submits that the specific portions of Gryaznov that the Examiner points to disclose the use of oligonucleotides that are **directly adjacent** to each other when bound to a template. However, Gryaznov fails to teach a method that utilizes oligonucleotide probes that are **not directly adjacent** (e.g., claims 44-48). Gryaznov also fails to teach a method that includes contacting the target polynucleotide with the **universal oligonucleotide** probe, the **wild-type polymorphism oligonucleotide** probe and the **mutant polymorphism oligonucleotide** probe to yield an autoligated oligonucleotide product including the universal oligonucleotide probe and **either** the mutant polymorphism oligonucleotide probe **or** the wild-type polymorphism oligonucleotide probe; and detecting the presence of the autoligated oligonucleotide product (e.g., claims 50-54 and 67-69). Furthermore, Gryaznov fails to teach a method for detecting a **genetic polymorphism** in a **target RNA** that includes contacting the target RNA with the **universal oligonucleotide** probe and the **mutant polymorphism oligonucleotide** probe to yield an autoligated oligonucleotide product including the universal oligonucleotide probe and the mutant polymorphism oligonucleotide probe; and detecting the presence of the autoligated oligonucleotide product (e.g., claims 56-60 and 70-72).

Applicant respectfully submits that Gryaznov fails to teach each and every element as set forth in the claim and therefore fails to anticipate the claims for the above mentioned reasons. Accordingly, the Examiner is respectfully requested to withdraw the rejections of the claims.

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 44-48, 50-54, 56-60, and 67-72 under 35 U.S.C. § 103 as being unpatentable over Northwestern (WO 96/35699). This rejection is respectfully traversed.

"To establish a *prima facie* case of obviousness . . . the prior art reference (or references when combined) must teach or suggest all the claim limitations." M.P.E.P. §706.02(j).

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness.

First, the Examiner characterized the invention as being "directed to a process of autoligation wherein autoligating oligonucleotides bind to a target solid-supported linked oligonucleotide target" (page 9 of Office Action mailed 22 April 2004). Applicant respectfully emphasizes that the target polynucleotide is not required to be a "solid-supported linked oligonucleotide target" as suggested by the Examiner.

Next, with regard to the obviousness rejection, the Examiner stated:

> "**Northwestern University '699** does not expressly disclose the particular target oligonucleotide or details of the oligonucleotide sequence to be autoligated to.
>
> It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the instant disclosed process to any solid-supported target including the targets taught by the instant claims. Any variations required to achieve a working test process with a different target sequence are deemed to have been within the purview of the ordinary practitioner seeking to optimize the prior art process, in the absence of a clearly convincing showing of unexpected results.
>
> Therefore, the instant claimed hybridization-based method of oligonucleotide sequence detection would have been obvious to one of ordinary skill in the art having the above cited reference before him at the time the invention was made" (page 9 of Office Action mailed 22 April 2004) (underlining added).

Applicant respectfully emphasizes that the Examiner has admitted that Northwestern University '669 (Northwestern) fails to teach or suggest all the claim language. Thus, Applicant respectfully submits that the Examiner has failed to present a *prima facie* case of obviousness. Further, Applicant respectfully submits that in the absence of a *prima facie* case of obviousness, a showing of unexpected results is not required.

Specifically, Northwestern fails to teach a method that utilizes oligonucleotide probes that are **not directly adjacent** (e.g., claims 44-48). Northwestern also fails to teach a method that includes contacting the target polynucleotide with the **universal oligonucleotide** probe, the

wild-type polymorphism oligonucleotide probe and the **mutant polymorphism oligonucleotide** probe to yield an autoligated oligonucleotide product including the universal oligonucleotide probe and **either** the mutant polymorphism oligonucleotide probe **or** the wild-type polymorphism oligonucleotide probe; and detecting the presence of the autoligated oligonucleotide product (e.g., claims 50-54 and 67-69). Furthermore, Northwestern fails to teach a method for detecting a **genetic polymorphism** in a **target RNA** that includes contacting the target RNA with the **universal oligonucleotide** probe and the **mutant polymorphism oligonucleotide** probe to yield an autoligated oligonucleotide product including the universal oligonucleotide probe and the mutant polymorphism oligonucleotide probe; and detecting the presence of the autoligated oligonucleotide product (e.g., claims 56-60 and 70-72). Moreover, Applicant respectfully submits that one of skill in the art would not have a reasonable expectation of success using a **target RNA**, because it is well known that helices formed when DNA binds RNA have a different structure than when DNA binds DNA.

Finally, Applicant respectfully submits that the Examiner relied on personal knowledge to reject the claims under 35 U.S.C. § 103 because the cited document fails to teach all of the claim limitations, as admitted by the Examiner, and the Examiner has not provided secondary documents that correct the failings of the cited document. Accordingly, Applicant respectfully asserts that, "when a rejection in an application is based on facts within the personal knowledge of an employee of the Office, the data shall be supported, when called for by the applicant, by the affidavit of such employee" (37 C.F.R. § 1.104(d)(2)). Therefore, in the event that the present rejection is maintained, Applicant respectfully requests an affidavit from the Examiner to support the rejection of the claims under 35 U.S.C. §103.

Accordingly, Applicant respectfully requests the Examiner to withdraw the rejections of the claims under 35 U.S.C. § 103.

Allowable Subject Matter

The Examiner indicated that claims 64-66 would be allowable if rewritten or amended to overcome the rejection under 35 U.S.C. § 112.

Applicant respectfully submits that the rejections of claims 64-66 under 35 U.S.C. § 112 have been addressed herein above, and requests that the claims be allowed.

New Claims

In a manner similar to claims 50-54 and 67-69, new claims 73-80 are directed to a method for detecting a genetic polymorphism in a target polynucleotide including contacting the target polynucleotide with the **universal oligonucleotide probe**, the **wild-type polymorphism oligonucleotide probe** and the **mutant polymorphism oligonucleotide probe** to yield an autoligated oligonucleotide product including the universal oligonucleotide probe and **either** the mutant polymorphism oligonucleotide probe **or** the wild-type polymorphism oligonucleotide probe and detecting the presence of the autoligated oligonucleotide product, which Applicant respectfully submits is not disclosed by the art cited in the present rejections. However, new claims 73-80 do not recite that the mutant polymorphism oligonucleotide probe is less than 7 nucleotides in length.

Entry and consideration of new claims 73-80 is respectfully requested.

Summary

It is respectfully submitted that all the pending claims are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicant's Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

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CERTIFICATE UNDER 37 CFR §1.10:
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The undersigned hereby certifies that the Transmittal Letter and the paper(s) and/or fee(s), as described hereinabove, are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to the Commissioner for Patents, Mail Stop Amendment, P.O. Box 1450, Alexandria, VA 22313-1450.

By: _____
Name: SARA E. OLSON

Amendments to the Drawings

The attached sheet of drawings includes changes to Figure 4a. This sheet replaces the original sheet that includes Figure 4a and Figure 4b. Figure 4a has been amended according to the instructions provided by the Examiner.